

Health Policy Report

IMPROVING PROTECTION FOR RESEARCH SUBJECTS

ROBERT STEINBROOK, M.D.

IN March 1996, Hoiyan Wan, a 19-year-old nursing student and a healthy volunteer in a study at the University of Rochester, died two days after undergoing bronchoscopy as part of the study. During the procedure, she received a fatal dose of lidocaine. A report that followed a state investigation criticized the researchers, the institutional review board (IRB), and the university.¹

Wan's death led to many changes at the University of Rochester, including the establishment of training programs for investigators and an overhaul and expansion of the university's IRBs. The university's response is sometimes cited as a model for other institutions facing similar problems with the protection of research subjects.

Clinical research in the United States is under scrutiny for many reasons. These include the deaths of subjects; problems with the review and monitoring of research at leading medical centers, such as those at Duke University and Johns Hopkins University; and concern that the trust of the public is being jeopardized by the financial interests of investigators and institutions.²⁻⁵ There are two conflicting views of the issue: that increased oversight of clinical research is essential and that greater protection of research subjects will interfere with medical progress. Mary Faith Marshall, director of the Program in Bioethics at the Kansas University Medical Center, said in an interview, "There seems to be widespread acknowledgment that while the system is not completely broken, it is not completely adequate either." Marshall also chairs the National Human Research Protections Advisory Committee, which provides advice to the Department of Health and Human Services. She noted, "These are our best institutions. It is hard to turn away and say this is just a blip on the screen, especially when the institutions themselves are acknowledging that they have problems."

In an earlier report, I discussed the suspension of federally supported research at the Johns Hopkins Medical Institutions.⁶ In this report, I consider the efforts being made to improve the protection of research subjects. These efforts include stronger federal oversight of research, accreditation of programs for the protection of research subjects, and increased

institutional and financial support of these programs, as well as improvements in training and standards for investigators and IRBs, better reporting of adverse events, and greater involvement and education of research participants and the public.

BACKGROUND

The increased scrutiny of clinical research comes at a time of rapid medical progress. The federal government and industry are spending more on biomedical research. Many new medications and devices are being developed. New approaches to treating disease, such as gene therapy and the therapeutic use of stem cells, hold great promise but may turn out to have unexpected adverse effects. Although no actual count is available, it is likely that more people are being asked to volunteer to participate as subjects in research.

Groups that review research protocols have to identify those that are most likely to put subjects at risk, as well as those that pose a low overall risk but that may be risky for a few subjects. The use of an experimental substance or an experimental challenge test requires careful scrutiny. Certain procedures, such as drawing blood, pose minimal risk, whereas others, such as bronchoscopy, colonoscopy, or cardiac catheterization, involve some risk, even in experienced hands. The use of healthy volunteers, particularly in studies that have no direct therapeutic potential, also requires particular attention. Although compliance with federal regulations is essential, "the goal is not to ensure compliance," Dr. Greg Koski, director of the Office for Human Research Protections, stated in an interview. "The goal is to prevent harm or injury to individuals who are taking part in research."

FEDERAL REGULATIONS

Investigators, IRBs, institutions, the sponsors of research, and the federal government share responsibility for protecting research subjects. Federal regulations governing the protection of research subjects are known as the "common rule," because they have been adopted by all the agencies that conduct or fund research involving human subjects.⁷ According to the common rule, investigators who conduct studies funded by these agencies must obtain voluntary, informed consent from subjects, and the risks of participation must be reasonable "in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." In addition, IRBs must conduct independent reviews of research. In 1998, there were an estimated 3000 to 5000 IRBs in the United States.⁸ Institutions conducting federally funded research must provide the Office for Human Research Protections with a written agreement — known as an "assur-

ance” — that they will comply with the regulations. The Food and Drug Administration (FDA) regulates the testing of new drugs and medical devices. The Office for Human Research Protections and the FDA both regulate some research.

PROBLEMS WITH THE SYSTEM

The agenda for protecting research subjects was established in the 1970s and 1980s by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and the President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Yet reports in recent years have identified persistent threats to the safety of subjects.⁸⁻¹³ “It is not as if we need another thoughtful analysis of things,” Koski said. “All we need in some respects is an action plan.”

The FDA requires similar standards for the protection of subjects in federally and privately funded research involving new drugs and medical devices; many institutions voluntarily apply the same standards to all federally and privately funded research. There is, however, no requirement that participants in privately sponsored research that falls outside the FDA’s jurisdiction receive the same protection that the federal regulations provide. In a report last year, the National Bioethics Advisory Commission stated that the potential difference in protection was “ethically indefensible” and “a fundamental flaw in the current oversight system.”⁹

IRBs have been criticized for reviewing too many protocols, reviewing protocols too quickly, having insufficient expertise, and providing too little training for investigators and board members. Ongoing review of approved research is minimal. Review boards may also have an inherent conflict of interest. If they are effective, they may block or delay the approval of research that is important to the financial health and reputation of the institutions that created them.

One reason for some of these problems is that the resources devoted to protecting subjects have not kept pace with the growth of federal and private expenditures for clinical research. From 1995 to 2000, the budget of the National Institutes of Health (NIH) doubled. President George W. Bush has requested \$27.3 billion for the NIH in fiscal year 2003, a 33 percent increase over the \$20.5 billion budget of fiscal year 2001.¹⁴

THE OFFICE FOR HUMAN RESEARCH PROTECTIONS

The Department of Health and Human Services established the Office for Human Research Protections in 2000. It replaced the NIH Office for Protection from Research Risks, which had less stature and visibility. The Office for Human Research Pro-

tections regulates institutions and other entities that conduct or oversee studies involving human subjects, including research in the biomedical, social, and behavioral sciences.¹⁵ The office has a budget of about \$7.3 million for fiscal year 2002, as compared with a budget of \$5.8 million in 2001 and \$2.7 million in 2000. Koski, who is the first director of the office, has sought to improve and to emphasize education and quality-improvement programs. His goal is for the office to have contact once every five years with all the entities that it regulates, in many cases through visits to institutions.

The Office for Human Research Protections has authority over research entities through their written assurances that they will comply with federal regulations. The assurances are being streamlined as a single type of assurance known as a “federal-wide” assurance, which Koski described as “a simple promise that if you are going to do the research and take the federal support, you are going to follow the rules.”

In addition to its educational and quality-improvement activities, the Office for Human Research Protections investigates complaints. When it identifies problems, it can require corrective actions. Examples include restrictions on specific investigators or projects, requirements for additional staff or educational programs, and suspension of specific protocols until they have been re-reviewed. The office has been criticized for shutting down research at institutions instead of imposing lesser sanctions. Koski, however, said that the current regulations provide “tremendous flexibility” and that “98 percent of compliance oversight activities do not result in shutting down an institution.”

The effect of the Office for Human Research Protections will not be clear for at least several years. Despite the changes Koski is making to differentiate the office from its predecessors, there is no certainty that it will be viewed more positively by the entities that it regulates. “I think [the office] has a very, very tough job on its hands,” said Dr. Jordan J. Cohen, president of the Association of American Medical Colleges. Cohen added that although the office “is really trying hard and doing a very good job,” it is still “a work in process.”

Although its staff and budget have increased, the Office for Human Research Protections has an ambitious agenda and many responsibilities. For example, the office is still compiling a list of all the IRBs in the United States that it oversees and is revising the assurances of compliance. As of early April 2002, 2270 IRBs at 1824 institutions had registered with the office. It has reduced its large backlog of compliance cases but still has many open cases. On January 1, 2001, there were 152 open cases; on December 31, there were 108.

During 2001, the Office for Human Research Protections conducted four site visits involving questions of compliance; some visits involved more than one case. The office, however, has been criticized for not conducting an on-site investigation of the death in May 2001 of Elaine Holden-Able, a 70-year-old control subject in a study sponsored by Case Western Reserve University and University Hospitals of Cleveland.¹⁶

Holden-Able, a nurse who was not employed at the hospital, was enrolled in a study of the metabolism of the amino acids methionine and homocysteine in people with Alzheimer's disease and age-matched healthy controls. The hypothesis was that these amino acids are metabolized differently in the two groups. The study was funded by a grant from Philip Morris and was conducted at the general clinical research center, which is funded by the NIH. On April 4, 2001, several hours after drinking a mixture of methionine, which is sold over the counter as a nutritional supplement, and orange juice, Holden-Able became severely ill. She became confused and vomited repeatedly. Severe respiratory distress developed, and she died on May 6. The exact cause of Holden-Able's death was not determined, but an internal investigation could not rule out an accidental overdose of methionine. This was considered the most reasonable explanation because she had very high blood levels of methionine. Subsequently, the medical center implemented new procedures for dispensing nutritional supplements.¹⁷⁻¹⁹

In August, the Office for Human Research Protections expressed concern about the conduct of the research. In November, after reviewing a report from the university and the medical center,¹⁹ as well as extensive records, the office "found no evidence to substantiate" its initial concern.²⁰ The office did not conduct an on-site investigation, as it had done in June 2001 after the death of Ellen Roche, a healthy volunteer in a federally funded study of asthma at Johns Hopkins University.⁶ The office "determined that a compliance-oversight site visit was not needed," according to Dr. Michael Carome, director of the office's Division of Compliance Oversight. The deaths of Roche and Holden-Able were the only deaths of healthy research subjects that were reported to the Office for Human Research Protections between January 2001 and March 2002.

THE FDA'S OFFICE FOR GOOD CLINICAL PRACTICE

In 2001, the FDA established the Office for Good Clinical Practice to coordinate its efforts to protect research subjects.²¹ Unlike the Office for Human Research Protections, which regulates primarily institutions, the Office for Good Clinical Practice regulates

research at many levels. It has oversight responsibility for about 50,000 active clinical investigators, 1000 commercial sponsors of research, and 2500 IRBs, according to its director, Dr. David Lepam. It also regulates groups that monitor trials and contract research organizations. Each year, FDA officials conduct approximately 1050 inspections and audits of clinical studies; about 700 involve investigators, 250 IRBs, and 100 institutional facilities. The agency regulates many more entities than it inspects or audits each year.

ACCREDITATION

Accreditation is meant to be more flexible and less onerous than regulation. The goal is not only to improve the quality of programs for protecting research subjects but also to use the process as a means of ensuring that institutions provide the same protections for participants in federally and privately funded research. With established performance standards and flexibility in how institutions meet them, there may be less need for direct government oversight and regulation. Thus, the standards established by the Association for the Accreditation of Human Research Protection Programs state that "The financing, structure and composition of the Research Review Unit, including the IRBs, are appropriate to the amount and nature of research reviewed" but do not specify appropriate resources.²² No matter how good the intentions behind accreditation standards, however, they can be perceived, like regulations, as burdensome and bureaucratic.

The Joint Committee on Accreditation of Healthcare Organizations and other groups have accredited health care organizations for many years. Although the accreditation of programs for the protection of research subjects has been recommended since the early 1980s, it was initiated in earnest only in the past year.¹¹ Two private organizations are involved. One is the National Committee for Quality Assurance, which accredits managed-care organizations and has started an accreditation program for the medical centers of the Department of Veterans Affairs.²³ The program is a response to the suspension of research involving human subjects at the West Los Angeles Veterans Affairs Medical Center in March 1999 because of its failure to correct long-standing problems with its systems for the protection of research subjects. Similar problems were subsequently identified at other Veterans Affairs medical centers.¹² The National Committee for Quality Assurance plans to offer accreditation to institutions outside the Veterans Affairs system as well.

In 2001, the Association of American Medical Colleges and six other groups founded the second private organization, the Association for the Accredi-

tation of Human Research Protection Programs.²⁴ In developing its standards, the association has drawn on the experience of the Association for Assessment and Accreditation of Laboratory Animal Care, which has provided voluntary accreditation since 1965.²⁵ The Association for the Accreditation of Human Research Protection Programs has conducted a pilot accreditation of the NIH intramural research programs. In February, it announced that it was ready to begin offering accreditation to other organizations that conduct or review research.²⁴

Marshall, the chair of the National Human Research Protections Advisory Committee, points out that although accreditation is voluntary, “the hope is that everyone will embrace it.” Cohen, the president of the Association of American Medical Colleges, anticipates that accreditation will “be sought by virtually everybody involved in human-subjects research.”

INSTITUTIONAL REVIEW BOARDS

Many institutions that have corrected serious problems with their programs for protecting research subjects, such as Johns Hopkins University and Duke University, have markedly increased their spending and increased the number of IRBs. The well-publicized problems have also prompted other institutions to review their programs. “My impression is that institutions have been going to school on the experiences that [Duke, Johns Hopkins, and other institutions] have gone through,” Cohen said. “The investments are in many cases sizable.”

Between 1999 and 2002, 7 of the 11 medical schools with the largest amounts of NIH support for research established additional IRBs (Table 1). Many institutions have developed educational programs for investigators and IRB members, hired additional staff, and placed senior officials in charge of programs for the protection of research subjects. The procedures used by investigational pharmacies have been strengthened to ensure that experimental medications and other substances are properly prepared and administered.

Another approach is to increase the use of external review boards, particularly for multicenter studies.²⁶ An external board would review the overall protocol for a multicenter study, thus decreasing the workload of the individual institutions. At specific sites, additional review might be provided either by the external review board or by the IRB. The goal is to avoid duplication of effort and to allow the review boards at an institution to have sufficient time to scrutinize other research. The National Cancer Institute has initiated a pilot program for a central IRB, which reviews institute-sponsored multicenter trials at the national level before they are reviewed locally. The program is described by Christian et al. elsewhere in

TABLE 1. NUMBER OF INSTITUTIONAL REVIEW BOARDS AT THE 11 MEDICAL SCHOOLS WITH THE LARGEST AMOUNTS OF RESEARCH SUPPORT FROM THE NATIONAL INSTITUTES OF HEALTH IN FISCAL YEAR 2000.*

SCHOOL	NO. OF INSTITUTIONAL REVIEW BOARDS		
	1995	1999	2002
Johns Hopkins University School of Medicine	2	2	5†
University of Pennsylvania School of Medicine	3	7	8
Washington University School of Medicine	4	4	10
University of California, San Francisco, School of Medicine	1	2	2
Yale University School of Medicine	1	1	2
Stanford University School of Medicine	2	4	4
University of California, Los Angeles, School of Medicine	3	3	3
University of Washington School of Medicine	3	3	4
Columbia University College of Physicians and Surgeons	1	1	1
University of Michigan Medical School	1	1	4
Duke University School of Medicine	1	1	5

*Data were provided by officials of the medical schools.

†In March 2002, two institutional review boards were consolidated, reducing the total from six to five.

this issue of the *Journal*.²⁷ The National Bioethics Advisory Commission has also advocated this approach.⁹ In addition, a number of academic medical centers that have had problems, including those at the University of Rochester and Johns Hopkins University, have sent some protocols to an independent review board, the Western Institutional Review Board of Olympia, Washington. It is uncertain, however, whether an external review board is as effective as a high-quality review board at a particular institution; comparative studies have not been performed.

Current federal regulations require that each IRB have “at least one member who is not otherwise affiliated with the institution” and “at least one member whose primary concerns are in nonscientific areas.”⁷ According to the National Bioethics Advisory Commission, the presence of 1 unaffiliated member may not be sufficient to avoid institutional influence, especially since many review boards have 15 to 21 members.⁹ The commission recommended that members who represent the perspectives of research participants, those who are unaffiliated with the institution, and those whose primary concerns are in nonscientific areas “should collectively represent at least 25 percent of the . . . membership.” It also stated that “members from all of these categories should be present each time an institutional review board meets.” These goals might be difficult to achieve, since such persons would have to be identified, provided

with appropriate education and training, and appointed in a way that allowed them to retain an independent voice.

The costs of improving IRBs and training investigators and staff are substantial. Financial support has been dependent on institutional discretion. Commercial sponsors of studies may earmark funds for institutional review, but in general, investigators have not been charged for the review of their protocols. The NIH and other federal agencies are considering whether to include as part of a grant specific funds for institutional review, instead of lumping the funds for this expense together with funds for other indirect costs. Koski has said that providing financial support for IRBs is “a major issue” and “a high priority.” In March 2002, the NIH announced a \$28.5 million program to provide institutions with “short-term interim support” for strengthening their oversight of clinical research.²⁸

FINES

Another way to ensure compliance with federal research regulations is to impose fines on clinical investigators or institutions found to be in violation. In 2000, Donna Shalala, who was then the secretary of the Department of Health and Human Services, proposed legislation that would have enabled the FDA to levy civil monetary penalties of up to \$250,000 per clinical investigator and \$1 million per institution for violations of informed-consent procedures and other major research practices.² Her proposal sparked strong opposition from medical schools and academic medical centers; it is not currently being pursued.

ONGOING REVIEW OF RESEARCH

Adverse events and complications occur after a study starts, not before. Although data and safety monitoring boards have an essential role in protecting research subjects, not all studies have such boards. IRBs often provide little continued oversight of research. Moreover, there is no centralized reporting system for adverse events in studies of experimental substances or off-label uses of approved medications. There is also no clear guidance about what should be reported and how. A centralized national reporting system might allow researchers to learn about safety issues that arose at other institutions. Data from such a system might have helped researchers at Johns Hopkins learn about the potential pulmonary toxicity of hexamethonium before — not after — Ellen Roche became fatally ill.⁶ Koski emphasizes the importance of a reporting system: “We need a national research safety system that actually captures information about ongoing research in real time and makes it accessible in an effective way to those who

need that information to protect those who are in research.” Although he considers the development of such a system “a high priority,” Koski acknowledges that there are formidable practical obstacles. These include issues involving intellectual property and the proprietary nature of some of the information that might be collected about experimental medications. Moreover, a national reporting system would require the establishment of standards for reporting and criteria for providing access to reported data.

CONCLUSIONS

The protection of research subjects has often been improved in response to crises, such as the revelations about the Tuskegee syphilis experiment in the 1970s²⁹ and the 1999 death of 18-year-old Jesse Gelsinger in a gene-transfer trial at the University of Pennsylvania.² It is uncertain whether there will be similar improvements in the years ahead. One reason is that it may be hard to determine whether the steps now being taken will actually make clinical research safer. “The whole system is pretty much data-free,” Helen McGough, director of the Human Subjects Division at the University of Washington in Seattle, said in an interview. “We have very poor data on the number of adverse events and whether there is any relation between the adverse events and the quantity and quality of IRB review.”

Although IRBs have been the focus of much criticism, they are only one part of the system for ensuring safety. Institutions, sponsors, the government, and particularly the clinical investigators who manage studies on a day-to-day basis also have essential roles. High-quality review boards may be necessary — but not sufficient — to protect research subjects. Since the objective is to prevent all deaths and serious injuries, it is inherently easy to fail and almost impossible to succeed fully.

Koski and the Office for Human Research Protections are trying to change the attitude that protecting research subjects and making progress in the prevention and treatment of disease are conflicting goals. “Protecting the participants in research is part of the research; it is not an administrative add-on,” Koski said. “We have to quit viewing the protection of subjects as an impediment. It is the system that provides the safeguards to preserve the trust that is necessary for people to be willing to participate.”

REFERENCES

1. Case report on death of University of Rochester student issued. Albany: New York State Department of Health, September 26, 1996.
2. Shalala D. Protecting research subjects — what must be done. *N Engl J Med* 2000;343:808-10.
3. Angell M. Is academic medicine for sale? *N Engl J Med* 2000;342:1516-8.
4. Biomedical research: HHS direction needed to address financial conflicts of interest. Washington, D.C.: General Accounting Office, November 2001. (GAO-02-89.)

5. Task Force on Financial Conflicts of Interest in Clinical Research. Protecting subjects, preserving trust, promoting progress — policy and guidelines for the oversight of individual financial interests in human subjects research. Washington, D.C.: Association of American Medical Colleges, December 2001. (Accessed April 12, 2002, at <http://www.aamc.org/members/coitf/>.)
6. Steinbrook R. Protecting research subjects — the crisis at Johns Hopkins. *N Engl J Med* 2002;346:716-20.
7. Protection of Human Subjects, 45 C.F.R. 46 (June 18, 1991).
8. Institutional review boards: a time for reform. Washington, D.C.: Department of Health and Human Services, June 1998. (OE1-01-97-00193.)
9. Ethical and policy issues in research involving human participants: Vol. 1. Bethesda, Md.: National Bioethics Advisory Commission, August 2001.
10. Protecting human research subjects: status of recommendations. Washington, D.C.: Department of Health and Human Services, April 2000. (OE1-01-97-00197.)
11. Institute of Medicine. Preserving public trust: accreditation and human research participant protection programs. Washington, D.C.: National Academy Press, 2001.
12. VA research: protections for human subjects need to be strengthened. Washington, D.C.: General Accounting Office, September 2000. (GAO/HEHS-00-155.)
13. Heinrich J. Human subjects research: HHS takes steps to strengthen protections, but concerns remain. Washington, D.C.: General Accounting Office, May 23, 2001. (GAO-01-775T.)
14. Press release for the FY 2003 President's budget. Bethesda, Md.: National Institutes of Health, February 4, 2002.
15. Koski G. Testimony before the Subcommittee on Oversight and Investigations, September 28, 2000. (Accessed April 12, 2002, at <http://veterans.house.gov/hearings/schedule106/sept00/9-28-00/gkoski.htm>.)
16. Kranish M. System for protecting humans in research faulted. *Boston Globe*. March 25, 2002:A1.
17. Solov D, McEnery R. Healthy woman died in UH Alzheimer's study hospital, CWRU cleared of significant wrongdoing; project suspended. *Cleveland Plain Dealer*. December 21, 2001:A1.
18. Joint statement from Case Western Reserve University and University Hospitals of Cleveland. Cleveland: Case Western Reserve University, December 2001. (Accessed April 12, 2002, at http://www.cwru.edu/pubaff/univcomm/state_cwruuh.htm.)
19. LaMantia C. Final report for adverse event investigation involving protocol entitled Methionine and Homocysteine Metabolism in Alzheimer's Disease Patients and Controls. Rockville, Md.: Office for Human Research Protections, August 7, 2001.
20. Borror KC. Human research subject protections under Multiple Project Assurance (MPA) M-1521: letter to Case Western Reserve University and University Hospitals of Cleveland. Rockville, Md.: Office for Human Research Protections, Department of Health and Human Services, November 30, 2001.
21. Establishment of the Office for Good Clinical Practice (OGCP). Washington, D.C.: Food and Drug Administration, October 26, 2001.
22. Final standards. Washington, D.C.: Association for the Accreditation of Human Research Protection Programs, 2002. (Accessed April 12, 2002, at <http://www.aahrpp.org/IRB.htm>.)
23. NCQA, VA launch first ever accreditation program for human research protection. Washington, D.C.: National Committee for Quality Assurance, August 28, 2001. (Accessed April 12, 2002, at <http://www.ncqa.org/communications/news/vahrpaplaunch.htm>.)
24. AAHRPP "open for business," ready to accept applications for accreditation. Press release of the Association for the Accreditation of Human Research Protection Programs, Washington, D.C., February 26, 2002.
25. About AAALAC. Rockville, Md.: Association for Assessment and Accreditation of Laboratory Animal Care, 2002. (Accessed April 12, 2002, at <http://www.aaalac.org/about.htm>.)
26. Burman WJ, Reves RR, Cohn DL, Schooley RT. Breaking the camel's back: multicenter clinical trials and local institutional review boards. *Ann Intern Med* 2001;134:152-7.
27. Christian MC, Goldberg JL, Killen J, et al. A central institutional review board for multi-institutional trials. *N Engl J Med* 2002;346:1405-8.
28. Human Subjects Research Enhancements Program. Bethesda, Md.: National Institutes of Health, March 5, 2002. (RFA OD-02-003.)
29. Tuskegee Syphilis Study Ad Hoc Advisory Panel. Final report. Washington, D.C.: Public Health Service, 1973.

Copyright © 2002 Massachusetts Medical Society.